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TENT COOPERATION TREA

PCT

NOTIFICATION OF ELECTION
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
 United States Patent and Trademark
 Office
 Box PCT
 Washington, D.C.20231
 ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 14 March 2000 (14.03.00)	
International application No. PCT/GB99/02042	Applicant's or agent's file reference IS/CP5787585
International filing date (day/month/year) 29 June 1999 (29.06.99)	Priority date (day/month/year) 29 June 1998 (29.06.98)
Applicant LEADLAY, Peter, Francis et al	

1. The designated Office is hereby notified of its election made:

 in the demand filed with the International Preliminary Examining Authority on:

27 January 2000 (27.01.00)

 in a notice effecting later election filed with the International Bureau on:2. The election was was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Olivia RANAIVOJAONA
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

REC'D 22 SEP 2000

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference IS/CP5787585	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB99/02042	International filing date (day/month/year) 29/06/1999	Priority date (day/month/year) 29/06/1998
International Patent Classification (IPC) or national classification and IPC C07H17/08		
Applicant BIOTICA TECHNOLOGY LIMITED et al.		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.		
2. This REPORT consists of a total of 8 sheets, including this cover sheet.		
<input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).		
These annexes consist of a total of sheets.		
3. This report contains indications relating to the following items:		
<ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input checked="" type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input checked="" type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 		

Date of submission of the demand 27/01/2000	Date of completion of this report 20.09.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer G. Willière Telephone No. +49 89 2399 8548



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/02042

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-58 as originally filed

Claims, No.:

1-25 as originally filed

Drawings, sheets:

1/12-12/12 as originally filed

2. The amendments have resulted in the cancellation of:

the description, pages:
 the claims, Nos.:
 the drawings, sheets:

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

see separate sheet

II. Priority

1. This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
 - copy of the earlier application whose priority has been claimed.
 - translation of the earlier application whose priority has been claimed.
2. This report has been established as if no priority had been claimed due to the fact that the priority claim has

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/02042

been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 2,3,5,6,8-22
	No:	Claims 1,4,7,23-25
Inventive step (IS)	Yes:	Claims 8-22
	No:	Claims 1-7,23-25

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/02042

Re Item I

Basis of the opinion

Sequence listing pages 1-79 filed with the letter of 8.12.1999 do not form part of the application (Rule 13^{ter}.1 (f) PCT).

Re Item II

Priority

The priority document in respect of the present application is at present not available to the International Preliminary Examination Authority. In consequence the current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the document D6 and D7 (please refer to item V, points 1 below) cited in the international search report could become relevant.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

- D1: WO 91 16334 A (ABBOTT LAB) 31 October 1991 (1991-10-31)
- D2: L.LIU ET AL.: 'Biosynthesis of 2-Nor-6-deoxyerythronolide B by Rationally Designed Domain Substitution.' JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 119, no. 43, 29 October 1997 (1997-10-29), pages 10553-10554, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DOCUMENT., US ISSN: 0002-7863
- D3: WO 98 01546 A (CORTES JESUS ;LEADLAY PETER F (GB); STAUNTON JAMES (GB); BIOTICA T) 15 January 1998 (1998-01-15) **cited in the application**
- D4: WO 98 01571 A (CORTES JESUS ;LEADLAY PETER F (GB); PACEY MICHAEL S (GB); STAUNTON) 15 January 1998 (1998-01-15) **cited in the application**
- D5: WO 95 08548 A (UNIV LELAND STANFORD JUNIOR ;JOHN INNES

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/02042

CENTRE (GB)) 30 March 1995 (1995-03-30) **cited in the application**

- D6: WO 98 49315 A (KOSAN BIOSCIENCES INC ;UNIV LELAND STANFORD JUNIOR (US)) 5 November 1998 (1998-11-05)
- D7: WO 99 35157 A (WU YONG JIN ;PFIZER PROD INC (US)) 15 July 1999 (1999-07-15), **cited in the application.**

2. The present application relates to 14-member macrolides having a methyl substitution in position C-13 (due to the use of an acetate starter unit) and to processes and enzyme systems, nucleic acids, vectors and cultures for preparing said compounds.
3. Compounds 5 and 7 of D1 (see page 7, lines 5 and 7) do not fall within the wording of claim 4 as being disclaimed thereof. However claim 1 still embraces said compounds. Moreover D1 discloses a process for preparing said compounds.

It follows that the subject-matter of claims 1, 7 and 25 is not novel (article 33(2) PCT) and does not involve an inventive step (article 33(3) PCT).

The compounds according to D1 have been prepared by genetically modifying the region responsible for the C-6 hydroxylation in the cytochrome P450 monooxygenase system. This is in contrast to the disclosure of the present application where the PKS loading module is adapted to load a malonyl residue which is subsequently decarboxylated to generate an acetate starter unit which is then transferred to an adjacent extension module. The subject-matter according to claims 10 to 24 is thus novel over D1.

None of the subject-matter according to present claims 2 to 6, 8 and 9 is disclosed in D1 nor is this subject-matter made obvious by this disclosure (article 33(2) and (3) PCT).

4. D2 discloses compound 3 at page 10554 and a process for preparing the same. The subject-matter of present claims 1, 4, 7, 23, 24 and 25 is thus not novel (article 33(2) PCT).

It appears that the subject-matter according to the system claims 10 to 19 and

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EXAMINATION REPORT - SEPARATE SHEET**

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claims 20-22 are novel when compared to D2 since the PKS loading module as presently claimed is adapted to load a malonyl residue which is subsequently decarboxylated to generate an acetate starter unit which is then transferred to an adjacent extension module. This is in contrast to the disclosure of D2 wherein an acyltransferase in module 6 (not the loading module) is replaced by a malonyl-specific acyltransferase.

None of the subject-matter according to present claims 2, 3, 5, 6, 8 and 9 is disclosed in D2 nor is this subject-matter made obvious by this disclosure (article 33(2) and (3) PCT).

5. D3 and D4 describe in general terms the production of further polyketides through genetically modified PKS units, i.e. by replacing the normal DEBS loading module by a loading module heterologous to the extension units which leads to a polyketide having an altered starter unit. D3 and D4 are silent with respect to C-13 methyl 14-member macrolides and are silent with respect to PKS loading modules adapted to load a malonyl residue subsequently being decarboxylated to generate an acetate starter unit which is then transferred to an adjacent extension module.

However D3 and D4 suggest a process for preparing C-13 methyl 14-member macrolides by teaching the skilled person to use a loading module which is specific for an acetate starter molecule. The subject-matter of present claim 7 (not disclosing specific steps used in said process) is thus believed not to involve an inventive step (article 33(3) PCT).

6. In addition to what has been disclosed in D3 and D4, D5 discloses the preparation of a novel host-vector system useful in the recombinant production of polyketides. However D5 is silent with respect to C-13 methyl 14-member macrolides and is silent with respect to PKS loading modules adapted to load a malonyl residue subsequently being decarboxylated to generate an acetate starter unit which is then transferred to an adjacent extension module.
7. The problem underlying the present alleged invention is the provision of a method for the preparation of further erythromycins at good expression levels and in the absence of erythromycins with different starter units, i.e. the development of a

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EXAMINATION REPORT - SEPARATE SHEET**

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method for avoiding the formation of mixtures of polyketides with both acetate and propionate starter units. This problem has been solved by replacing the natural loading domains by methylmalonyl-CoA loading modules which specifically bind their starter unit and subsequently decarboxylate said starter unit to form a propionate unit which is then transferred to the extension modules.

None of the cited documents D1 to D5 suggest this solution, nor was this problem addressed to in said documents. It is thus believed the subject-matter according to claims 8 to 22 involves an inventive step as required by article 33(3) PCT.

The subject-matter according to claims 23 to 25 (lacking novelty) may only be regarded as to involve an inventive step in combination with novel subject-matter (article 33(3) PCT).

8. The subject-matter relating to novel C-13 methyl erythromycin derivatives according to claims 1 to 6 is not believed to involve an inventive step (article 33(3) PCT). Indeed said subject-matter includes compounds merely differing from those of the prior art by minor modifications. Moreover the prior art shows that the variability of the substitutions to be inserted at different positions within the 14-member macrolide without losing the specific properties of the compounds is apparently not limited.

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
D6	05.11.1998	30.04.1998	30.04.1997 05.05.1998
D7	15.07.1999	21.12.1998	02.01.1998

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/02042

Re Item VIII

Certain observations on the international application

1. Claims 10 to 12 refer to PKS multi enzyme systems wherein at least one of the extension modules is **not naturally associated** with a loading module that effects decarboxylation. This wording renders said claims unclear (article 6 PCT). The Applicant is requested to rewrite said claims by using **technical terms of the invention** (Article 6.3 (a) PCT).
2. The use of the word "substantially" in connection with a list of sequences (see figure 2) renders the scope of claim 15 unclear (Article 6 PCT).
3. The process claims 7 to 9 do not define the subject-matter for which protection is sought by using those technical features of the invention which are necessary for the definition of the claimed subject matter, i.e. for the definition of a **process** (Rule 6.3 (b) PCT).
4. Claim 4, disclaiming merely 2 specific compounds, is dependent on claim 1 which disclaims 3 specific compounds. Consequently it appears that some compounds according to claim 4 are not embraced by claim 1. The wording of said claims should thus be revised as it is actually not clear whether claim 4 is, or is not dependent from claim 1 (article 6 PCT).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference IS/CP5787585	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 99/ 02042	International filing date (day/month/year) 29/06/1999	(Earliest) Priority Date (day/month/year) 29/06/1998
Applicant BIOTICA TECHNOLOGY LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
 - contained in the international application in written form.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority in written form.
 - furnished subsequently to this Authority in computer readable form.
 - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).

3. Unity of invention is lacking (see Box II).

4. With regard to the title,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- the text is approved as submitted by the applicant
- the text has been established, according to Rule 38(1)(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02042

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H17/08 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91 16334 A (ABBOTT LAB) 31 October 1991 (1991-10-31) the whole document, but especially page 7, 6-Deoxy-15-norerythromycins A-D. More especially 6-Deoxy-15-norerythromycins A and C ---- -/-	1-9

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

5 January 2000

20/01/2000

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx: 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Scott, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02042

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	L.LIN ET AL.: "Biosynthesis of 2-Nor-6-deoxyerythronolide B by Rationally Designed Domain Substitution." JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 119, no. 43, 29 October 1997 (1997-10-29), pages 10553-10554, XP002121612 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863	1-14
X	the whole document, but especially compound 3 ---	1,4,7
Y	WO 98 01546 A (CORTES JESUS ;LEADLAY PETER F (GB); STAUNTON JAMES (GB); BIOTICA T) 15 January 1998 (1998-01-15) cited in the application	1-17
X	the whole document ---	1,4,7
Y	WO 98 01571 A (CORTES JESUS ;LEADLAY PETER F (GB); PACEY MICHAEL S (GB); STAUNTON) 15 January 1998 (1998-01-15) cited in the application	1-17
Y	the whole document WO 95 08548 A (UNIV LELAND STANFORD JUNIOR ;JOHN INNES CENTRE (GB)) 30 March 1995 (1995-03-30) cited in the application	1-17
P,X	the whole document WO 98 49315 A (KOSAN BIOSCIENCES INC ;UNIV LELAND STANFORD JUNIOR (US)) 5 November 1998 (1998-11-05) the whole document, but especially claims 1-28 and figure 6/table 2, all compounds containing "nor" ---	1-17
E	the whole document WO 99 35157 A (WU YONG JIN ;PFIZER PROD INC (US)) 15 July 1999 (1999-07-15) -----	1,4,7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

GB 99/02042

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9116334	A	31-10-1991	US 5141926 A		25-08-1992
			CA 2080583 A		19-10-1991
			EP 0525083 A		03-02-1993
			JP 2587562 B		05-03-1997
			JP 5504890 T		29-07-1993
			KR 9608668 B		28-06-1996
			PT 97390 A		31-01-1992

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			AU 3451497 A		02-02-1998
			CA 2259420 A		15-01-1998
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			CN 1229438 A		22-09-1999
			EP 0909327 A		21-04-1999
			EP 0910633 A		28-04-1999
			WO 9801571 A		15-01-1998
			GB 2331518 A		26-05-1999
			NO 990012 A		23-02-1999
			PL 331285 A		05-07-1999
			AU 7666198 A		30-12-1998
			WO 9854308 A		03-12-1998

WO 9801571	A	15-01-1998	AU 3450997 A		02-02-1998
			AU 3451497 A		02-02-1998
			CA 2259420 A		15-01-1998
			CA 2259463 A		15-01-1998
			CN 1229438 A		22-09-1999
			EP 0909327 A		21-04-1999
			EP 0910633 A		28-04-1999
			WO 9801546 A		15-01-1998
			GB 2331518 A		26-05-1999
			NO 990012 A		23-02-1999
			PL 331285 A		05-07-1999
			AU 7666198 A		30-12-1998
			WO 9854308 A		03-12-1998

WO 9508548	A	30-03-1995	US 5672491 A		30-09-1997
			AU 678058 B		15-05-1997
			AU 7731794 A		10-04-1995
			CA 2171629 A		30-03-1995
			EP 0725778 A		14-08-1996
			JP 9505983 T		17-06-1997
			US 5712146 A		27-01-1998
			US 5830750 A		03-11-1998
			US 5843718 A		01-12-1998
			US 5962290 A		05-10-1999

WO 9849315	A	05-11-1998	AU 7172298 A		24-11-1998

WO 9935157	A	15-07-1999	AU 1501599 A		26-07-1999



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07H 17/08, A61K 31/70		A3	(11) International Publication Number: WO 00/00500 (43) International Publication Date: 6 January 2000 (06.01.00)
(21) International Application Number: PCT/GB99/02042			(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 29 June 1999 (29.06.99)			
(30) Priority Data: 9814006.4 29 June 1998 (29.06.98) GB			
(71) Applicants (<i>for all designated States except US</i>): BIOTICA TECHNOLOGY LIMITED [GB/GB]; 112 Hills Road, Cambridge CB2 1PH (GB). PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).			
(72) Inventors; and			Published
(75) Inventors/Applicants (<i>for US only</i>): LEADLAY, Peter, Francis [GB/GB]; 17 Clarendon Road, Cambridge CB2 2BH (GB). STAUNTON, James [GB/GB]; 29 Porson Road, Cambridge CB2 ET (GB). CORTES, Jesus [GB/GB]; 26 Cambanks, Union Lane, Cambridge CB4 1PZ (GB). MCARTHUR, Hamish, Alastair, Irvine [GB/US]; 19 Pheasant Run Drive, Gales Ferry, CT 06335 (US).			<i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(74) Agents: STUART, Ian et al.; Mewburn Ellis, York House, 23 Kingsway, London WC2B 6HP (GB).			(88) Date of publication of the international search report: 16 March 2000 (16.03.00)

(54) Title: POLYKETIDES AND THEIR SYNTHESIS

(57) Abstract

A polyketide synthase ("PKS") of Type I is a complex multienzyme including a loading domain linked to a multiplicity of extension domains. The first extension module receives an acyl starter unit from the loading domain and each extension module adds a further ketide unit which may undergo processing (e.g. reduction). We have found that the Ksq domain possessed by some PKS's has decarboxylating activity, e.g. generating (substituted) acyl from (substituted) malonyl. The CLF domain of type II PKS's has similar activity. By inserting loading modules including such domains into PKS's not normally possessing them it is possible to control the starter units used.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02042

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07H17/08 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	<p>WO 91 16334 A (ABBOTT LAB) 31 October 1991 (1991-10-31) the whole document, but especially page 7, 6-Deoxy-15-norerythromycins A-D. More especially 6-Deoxy-15-norerythromycins A and C</p> <p>---</p> <p>-/-</p>	1-9

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

5 January 2000

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/GB 99/02042

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	L.LIN ET AL.: "Biosynthesis of 2-Nor-6-deoxyerythronolide B by Rationally Designed Domain Substitution." JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 119, no. 43, 29 October 1997 (1997-10-29), pages 10553-10554, XP002121612 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863	1-14
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